Congenital Hyperinsulinism - Treatment

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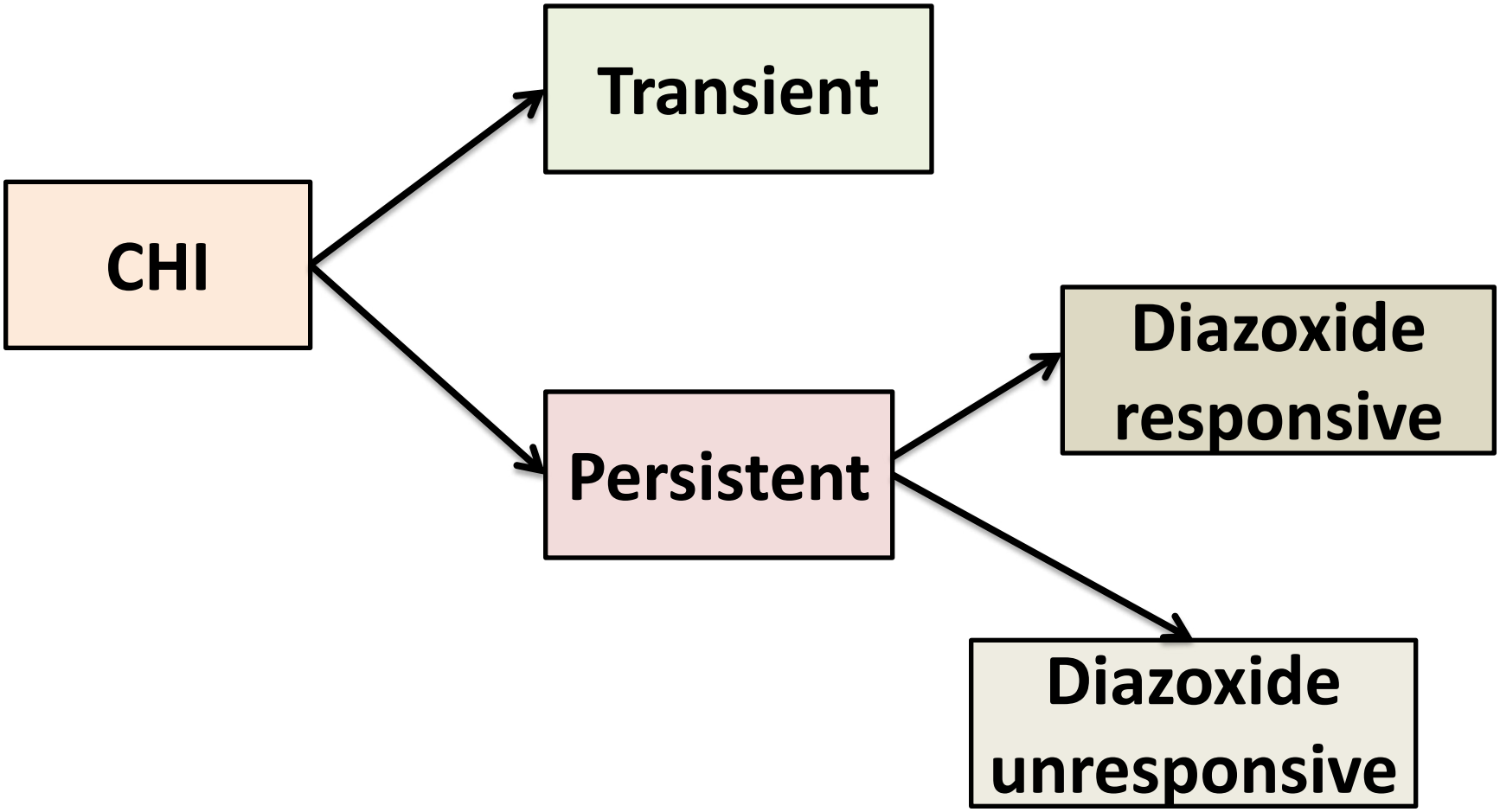
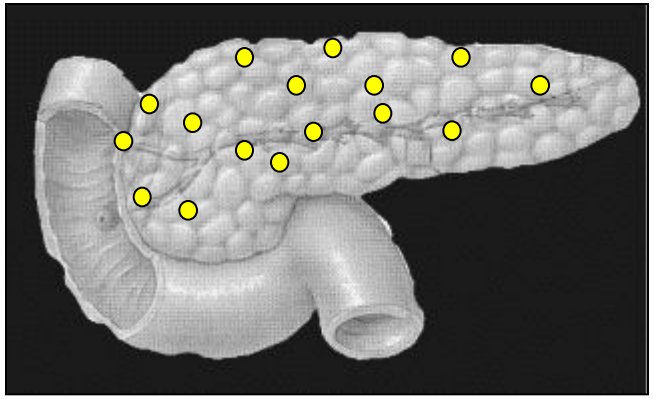
CHI


CHI
Transient
Persistent
Diazoxide responsive
Diazoxide unresponsive

Histological subtypes

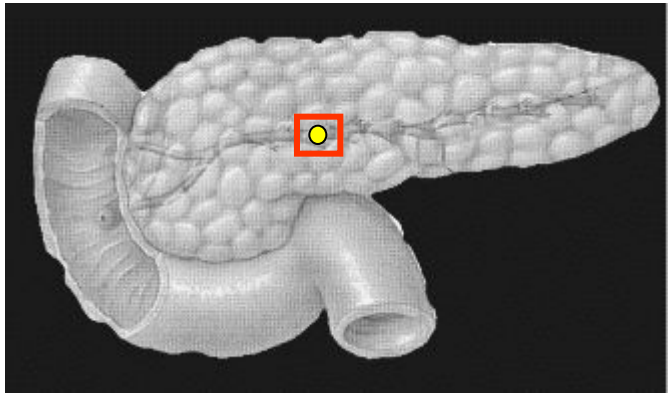
Diffuse disease

Histological abnormalities in beta cells throughout the pancreas



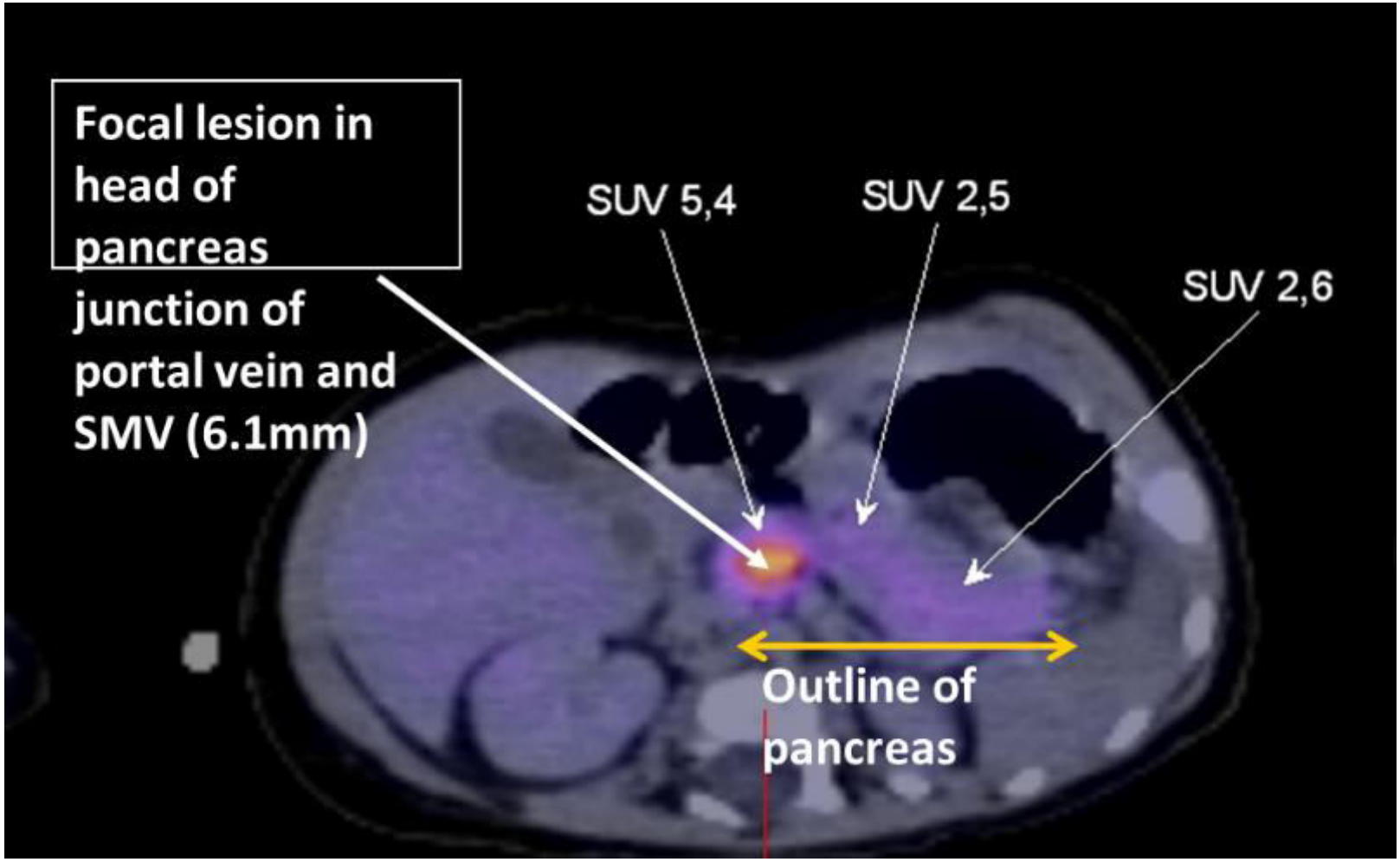
Focal disease

Focal islet-cell hyperplasia within the lesion, rest of the pancreas normal

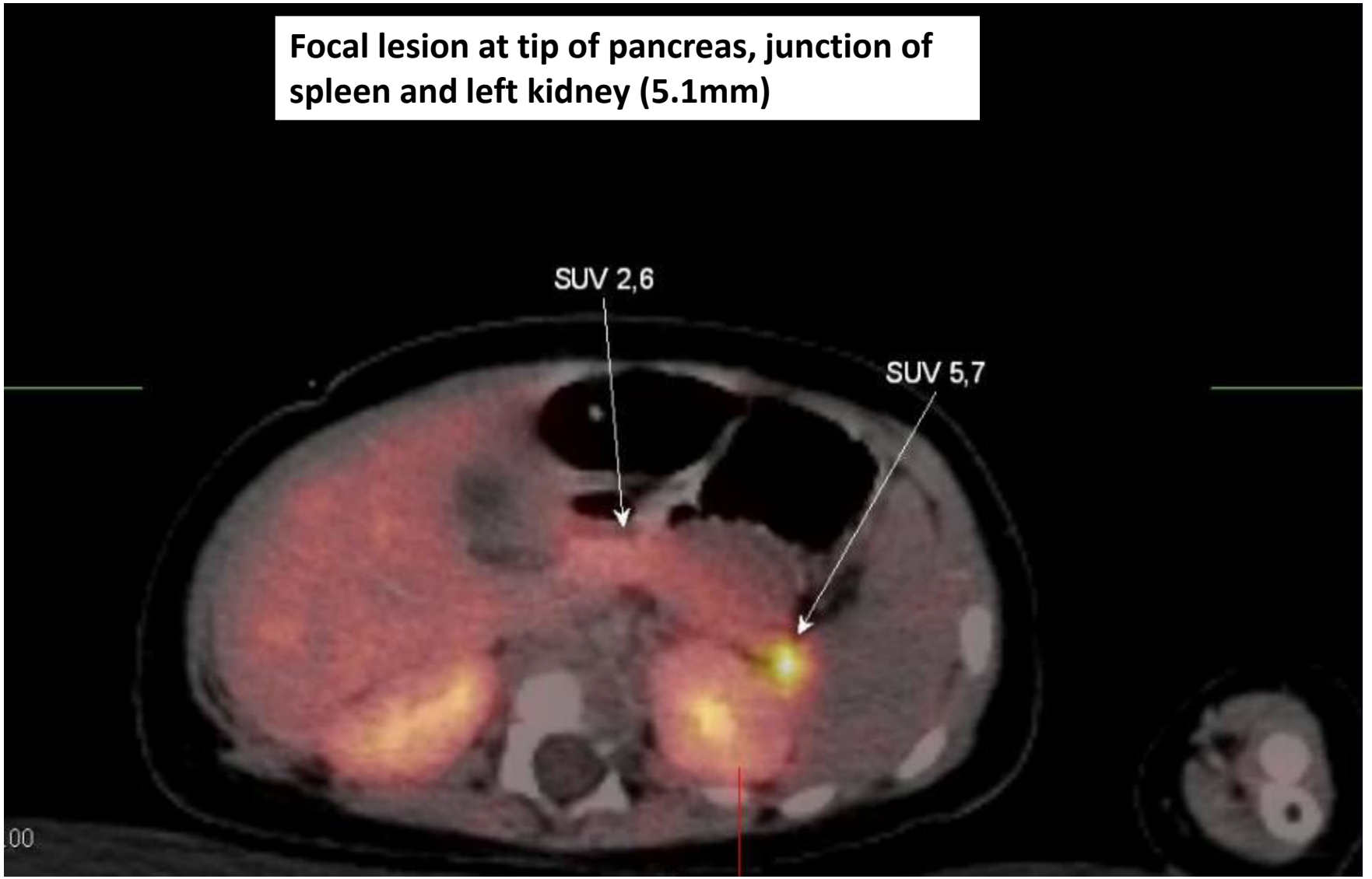


18F-DOPA-PET/CT

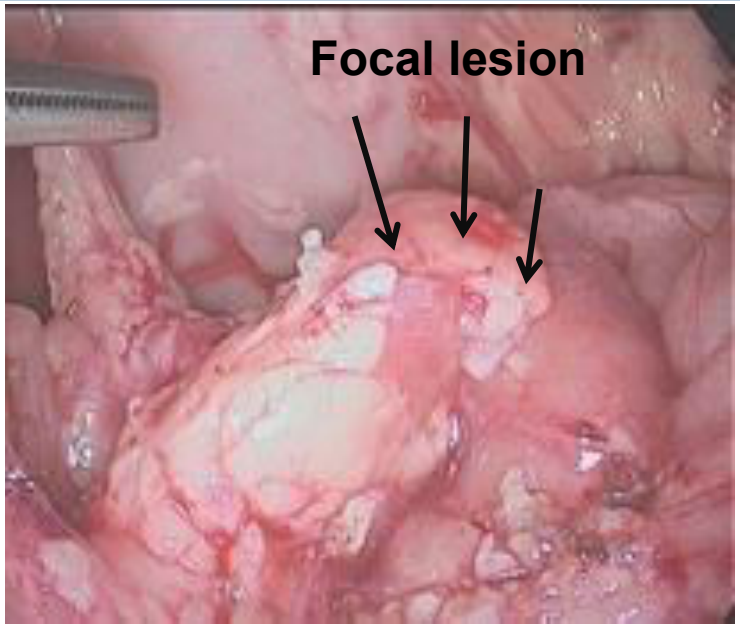
18-F-DOPA PET/CT Scan

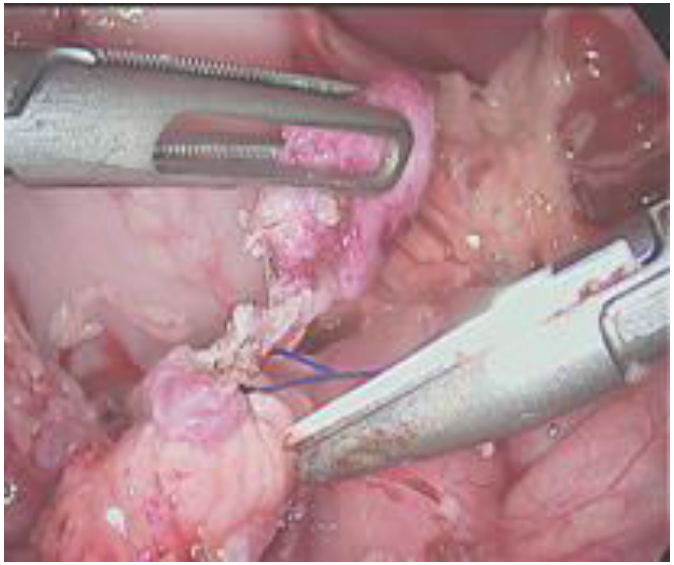


18-F-DOPA PET/CT Scan

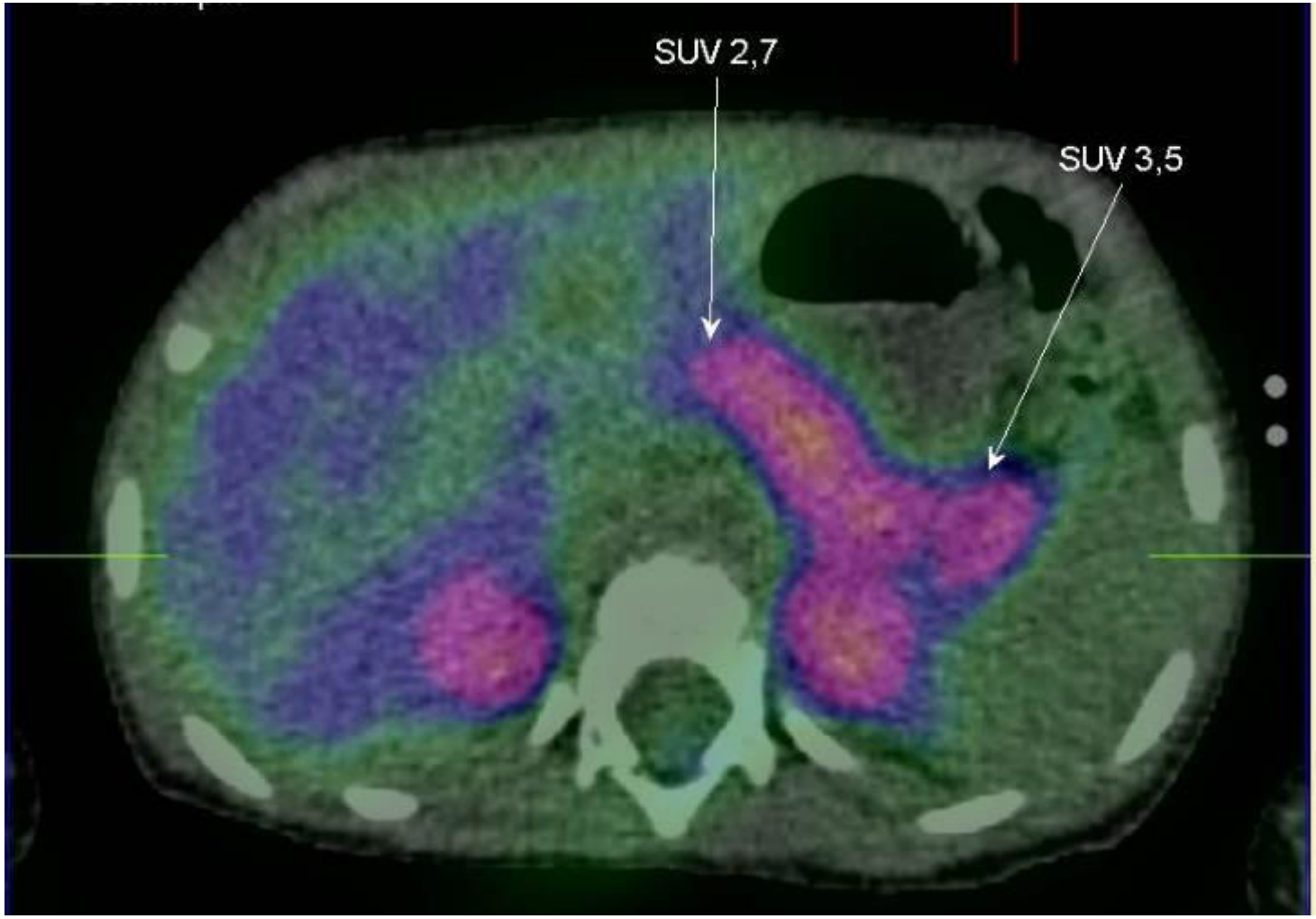


Laparoscopic Surgery





Diffuse disease



Surgery

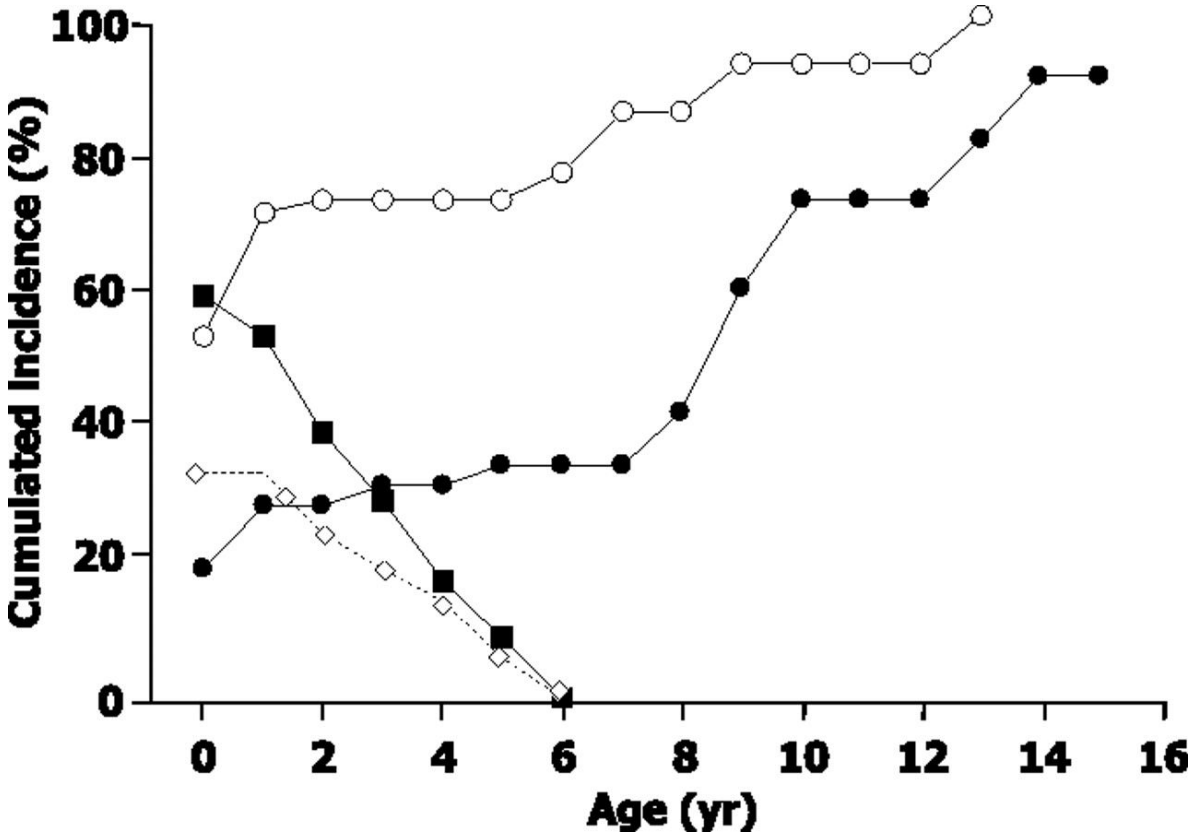
- Severe diffuse CHI – unresponsive to diazoxide/octreotide
- 95% to 98% **pancreatectomy**
- Post op complications – ongoing hypoglycaemia, **diabetes mellitus**, exocrine pancreatic insufficiency

Surgery - Outcomes

- 105 children (58 diffuse)
- Diffuse - 59% still had hypoglycemia requiring medical treatments (resolved by 5 years)
- Hyperglycaemia in 53% immediately after surgery & 100% by 13 years of age
- The cumulative incidence of insulin-treated patients was 42% at 8 years & 91% at 14 years of age

Glucose Metabolism in 105 Children and Adolescents After Pancreatectomy for Congenital Hyperinsulinism. Jacques Beltrand, Marylène Caquard, Jean-Baptiste Arnoux, Kathleen Laborde, Gilberto Velho, Virginie Verkarre, Jacques Rahier, Francis Brunelle, Claire Nihoul-Fékété, Jean-Marie Saudubray, Jean-Jacques Robert, and Pascale de Lonlay. Diabetes Care. 2012 Feb; 35(2): 198–203.

Surgery - Outcomes



Glucose Metabolism in 105 Children and Adolescents After Pancreatectomy for Congenital Hyperinsulinism. Jacques Beltrand, Marylène Caquard, Jean-Baptiste Arnoux, Kathleen Laborde, Gilberto Velho, Virginie Verkarre, Jacques Rahier, Francis Brunelle, Claire Nihoul-Fékété, Jean-Marie Saudubray, Jean-Jacques Robert, and Pascale de Lonlay. Diabetes Care. 2012 Feb; 35(2): 198–203.

Long term Medical Treatment

- Review of case series/reports on **619** CHI patients (till 2013)

Diazoxide (84%)

- Mean dose of diazoxide: 12.5 (±4.3) mg/kg/day (range 2– 60)
- Mean duration of treatment until remission: 5 years
- Side effects of diazoxide were usually not severe

Long-term medical treatment in congenital hyperinsulinism: a descriptive analysis in a large cohort of patients from different clinical centers. *Alena Welters, Christian Lerch, Sebastian Kummer, Jan Marquard, Burak Salgin, Ertan Mayatepek, and Thomas Meissner. Orphanet Journal of Rare Diseases (2015) 10:150*

Long term Medical Treatment

Somatostatin analogues (16%)

- Mean dose of octreotide 14.9 (±7.5) µg/kg/d (range 2.3– 50)
- Lanreotide 67.3 (±39.8) mg/month (range 10–120)
- Mean duration of treatment until remission: 4 years
- Frequent side effects: tachyphylaxis and mild GI symptoms
- The risk of persistent growth deceleration was low (<5 %)

Others: Glucagon, Ca channel blockers, high calorie diet

Long-term medical treatment in congenital hyperinsulinism: a descriptive analysis in a large cohort of patients from different clinical centers. Alena Welters, Christian Lerch, Sebastian Kummer, Jan Marquard, Burak Salgin, Ertan Mayatepek, and Thomas Meissner. Orphanet Journal of Rare Diseases (2015) 10:150

Newer/Futuristic Therapeutic options

- Long acting somatostatin analogues
- mTOR inhibitors
- GLP1 receptor antagonists
- Long-acting soluble glucagon
- Specific somatostatin receptor agonists
- Insulin receptor antibody

Long acting Somatostatin Analogues

- Selective binding affinity for SSTR 2 and 5
- Unlicensed for CHI

Somatuline autogel (Lanreotide)

- 30,60,90mg prefilled syringe
- Rapid-release phase, followed by a long-lasting phase of slow release

Sandostatin LAR (octreotide)

- 10,20,30mg vials
- Slow release during the first 2 weeks and then increases quickly to reach a stable phase between 3 and 4 weeks

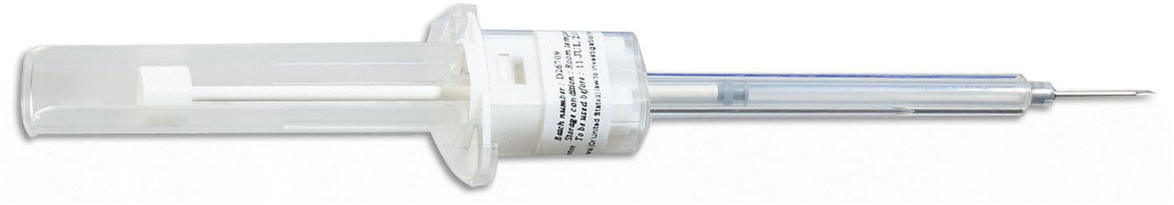
Long acting Somatostatin Analogues

- For patients who do not respond or tolerate diazoxide after a trial of s/c Octreotide

<u>Starting dosage</u>

Lanreotide 30–60 mg deep subcutaneous every 4 weeks

Sandostatin-LAR 10 mg intramuscularly every 4 weeks



Benefits

- Better quality of life
- No more daily injections
- Less trauma and pain
- More freedom for child and parents
- Easier to travel – car journeys, flying, holidays
- Cost effective

Side-effects

- Allergic type reactions / local reactions
- GI side effects - anorexia, nausea, abdominal pain, bloating, flatulence, loose stools
- Decrease gallbladder contractility - cholestasis, hepatic dysfunction and gall stones
- Suppression of growth and thyroid hormones (rare)
- Risk of NEC in neonates
- Tachyphylaxis

Monitoring

- Regular blood glucose monitoring and/or CGMS
- Liver function every 4–6 weeks
- Abdominal ultrasound every 3–6 months
- If (asymptomatic) cholelithiasis is present, ursodeoxycholic acid (UDCA) could be tried
- Growth and thyroid function at least 6-monthly

Studies…

- *Modan-Moses D et al. Treatment of Congenital Hyperinsulinism with Lanreotide Acetate. J Clin Endocrin Metab, 2011 Aug;96(8):2312-7.*
- *Le Quan Sang KH et al. Successful treatment of congenital hyperinsulinism with long-acting release octreotide. Eur J Endocrinol. 2012 Feb;166(2):333-9.*
- *Kühnen P, Marquard J, Ernert A, Meissner T, Raile K, Wannenmacher G, Blankenstein O. Long-term lanreotide treatment in six patients with congenital hyperinsulinism. Horm Res Paediatr. 2012;78(2):106-12.*
- *Use of Long-Acting Somatostatin Analogue (Lanreotide) in an Adolescent with Diazoxide-Responsive Congenital Hyperinsulinism and Its Psychological Impact. Shah P, Rahman SA, McElroy S, Gilbert C, Morgan K, Hinchey L, Senniappan S, Levy H, Amin R, Hussain K. Horm Res Paediatr. 2015;84(5):355-60.*
- *Corda H, Kummer S, Welters A, Teig N, Klee D, Mayatepek E, Meissner T. Treatment with long-acting lanreotide autogel in early infancy in patients with severe neonatal hyperinsulinism. Orphanet J Rare Dis. 2017 Jun 2;12(1)*
- *Dastamani A, Güemes M, Pitfield C, Morgan K, Rajab M, Rottenburger C, Bomanji J, De Coppi P, Dattani M, Shah P. The Use of a Long-Acting Somatostatin Analogue (Lanreotide) in Three Children with Focal Forms of Congenital Hyperinsulinaemic Hypoglycaemia. Horm Res Paediatr. 2018 Aug 16:1-6.*

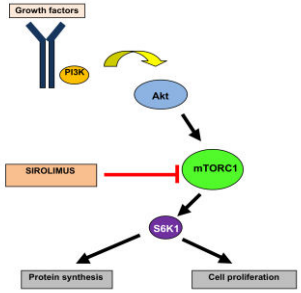
Evidence..

- **27** patients (2 focal) in 6 centres [retrospective]
- Beneficial in **89%** [not all had CGMS]
- **48%** some side effects (mainly raised liver enzymes)
- 11% discontinued due to side effects (local abscess, raised ALT)
- Starting age **2m-17 years**
- Duration of treatment **1-72 months** (average 18 months)
- Dose **5mg-90mg**/month
- Majority on combined therapy with enriched feeds/Diazoxide

Van der Steen, van Albada ME, Mohnike K, Christesen HT, Empting S, Salomon-Estebanez M, Greve Rasmussen A, Verrijn Stuart A, van der Linde AAA, Banerjee I, Boot AM1. A Multicenter Experience with Long-Acting Somatostatin Analogues in Patients with Congenital Hyperinsulinism. Horm Res Paediatr. 2018;89(2):82-89

mTOR inhibitors

- Used in insulinoma in adults and paediatric post-transplant
- Noted to be beneficial in some severe diffuse CHI patients unresponsive to diazoxide/octreotide
- **Sirolimus** (oral): starting dose 0.5mg/m2/day (max 3mg/m2/day), aim serum level 5-15ng/ml
- Immunosuppressive - close monitoring of serum levels, blood counts, oral cavity, renal and liver function & lipids



Case reports/series..

Sirolimus Therapy in Infants with Severe Hyperinsulinemic Hypoglycemia. *Senthil Senniappan, M.D., Sanda Alexandrescu, M.D., Nina Tatevian, M.D., Pratik Shah, M.D., Ved Arya, M.D., Sarah Flanagan, Ph.D., Sian Ellard, Ph.D., Dyanne Rampling, F.I.B.M.S., Michael Ashworth, M.D., Robert E. Brown, M.D., and Khalid Hussain, M.D.* ***N Engl J Med 2014; 370:1131-1137***

Sirolimus therapy in a child with partially diazoxide-responsive hyperinsulinaemic hypoglycaemia.
Loke KY[1], Anjian AS[2], Yijuan YL[2], Ho Wei Li C[2], Güemes M[3], Hussain K[3.] Endocrinol Diabetes Metab Case Rep. 2016;2016. pii: 16-0043.

A NOVEL HOMOZYGOUS MUTATION IN THE KCNJ11 GENE p.F315I OF A NEONATE WITH CONGENITAL HYPERINSULINISM AND SUCCESFUL MANAGEMENT BY SIROLIMUS. *Ünal S, Gönülal D, Uçaktürk A, Siyah Bilgin B, Flanagan SE, Gürbüz F, Tayfun M, Elmaoğulları S, Araslı A, Demirel F, Ellard S, Hussain K. J Clin Res Pediatr Endocrinol. 2016 May 16. doi: 10.4274/jcrpe.2773*

Severe Hyperinsulinemic Hypoglycemia in a Neonate: Response to Sirolimus Therapy. *Méder Ü, Bokodi G, Balogh L, Körner A, Szabó M, Pruhova S, Szabó AJ. Pediatrics. 2015 Nov;136(5):e1369-72. doi: 10.1542/peds.2014-4200.*

Sirolimus therapy in a patient with severe hyperinsulinaemic hypoglycaemia due to a compound heterozygous ABCC8 gene mutation.
Shah P, Arya VB, Flanagan SE, Morgan K, Ellard S, Senniappan S, Hussain K. J Pediatr Endocrinol Metab. 2015 May;28(5-6):695-9. doi: 10.1515/jpem-2014-0371.

Efficacy and safety of sirolimus in a neonate with persistent hypoglycaemia following near-total pancreatectomy for hyperinsulinaemic hypoglycaemia. *Abraham MB et al., J Pediatr Endocrinol Metab. 2015 Nov 1;28(11-12):1391-8. doi: 10.1515/jpem-2015-0094.*

Sirolimus therapy for congenital hyperinsulinism in an infant with a novel homozygous KCNJ11 mutation.
Korula S, Chapla A, Priyambada L, Mathai S, Simon A. J Pediatr Endocrinol Metab. 2018 Jan 26;31(1):87-89

Sirolimus Therapy in Congenital Hyperinsulinism: A Successful Experience Beyond Infancy. *Minute M1, Patti G2, Tornese G3, Faleschini E4, Zuiani C2, Ventura A3. Pediatrics. 2015 Nov;136(5):e1373-6. doi: 10.1542/peds.2015-1132*

Case reports/series…

Sirolimus precipitating diabetes mellitus in a patient with congenital hyperinsulinaemic hypoglycaemia due to autosomal dominant ABCC8 mutation. *Dastamani A, Güemes M, Walker J, Shah P, Hussain K.*
J Pediatr Endocrinol Metab. 2017 Oct 26;30(11):

Sirolimus in the treatment of three infants with diffuse congenital hyperinsulinism.
Al-Balwi R, Al-Atawi M, Al-Otaibi A, Babiker O, Al-Mutair A. J Pediatr Endocrinol Metab. 2017 Aug 28;30(9):

mTOR Inhibitors for the Treatment of Severe Congenital Hyperinsulinism: Perspectives on Limited Therapeutic Success.
Szymanowski M, Estebanez MS, Padidela R, Han B, Mosinska K, Stevens A, Damaj L, Pihan-Le Bars F, Lascouts E, Reynaud R, Ferreira C, Bansept C, de Lonlay P, Saint-Martin C, Dunne MJ, Banerjee I, Arnoux JB.
J Clin Endocrinol Metab. 2016 Dec;101(12):

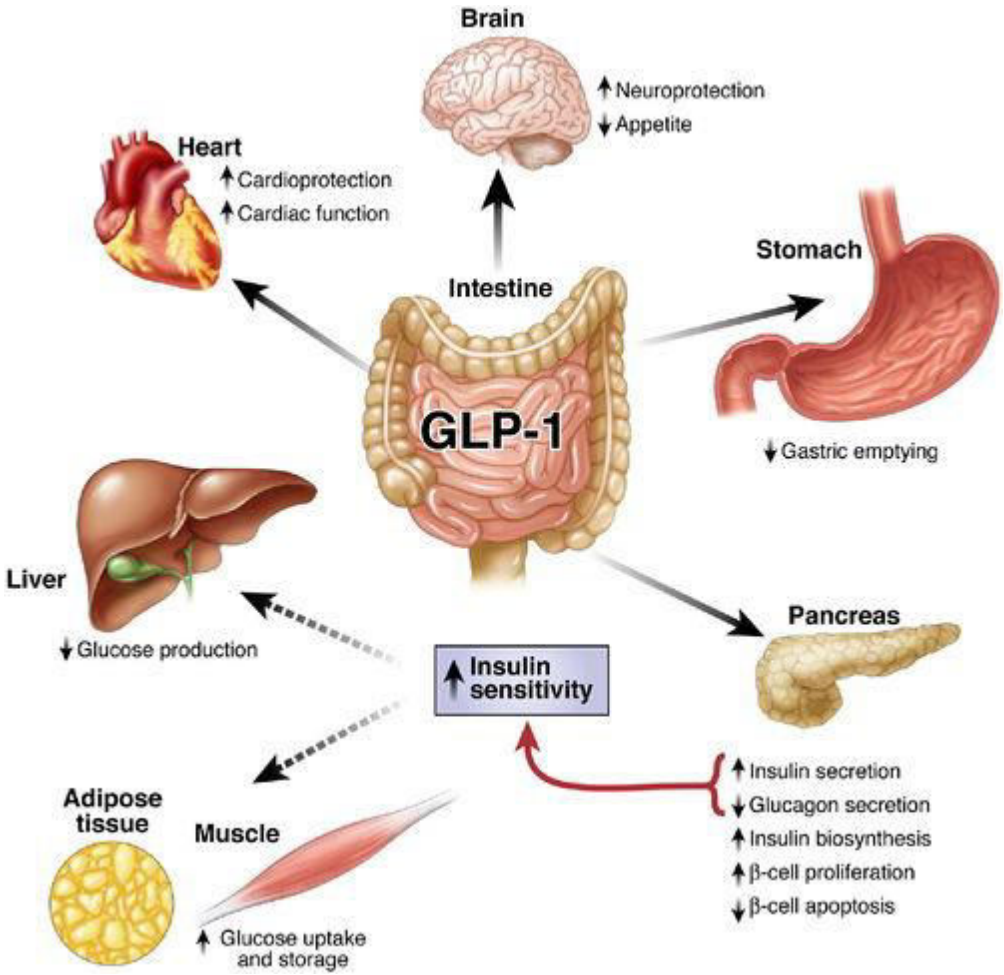
Extreme caution on the use of sirolimus for the congenital hyperinsulinism in infancy patient.
Banerjee I, De Leon D, Dunne MJ. Orphanet J Rare Dis. 2017 Apr 14;12(1):70

Sirolimus-Induced Hepatitis in Two Patients with Hyperinsulinemic Hypoglycemia
Haliloğlu B, Tüzün H, Flanagan SE, Çelik M, Kaya A, Ellard S, Özbek MN. J Clin Res Pediatr Endocrinol. 2018 Jul 31;10(3)

GLP-1

- Glucagon-like peptide-1 : produced in L-cells of the intestine in response to meal
- **Stimulates insulin secretion** & inhibits glucagon secretion
- Also inhibits hepatic glucose production, gastric emptying, and appetite

GLP-1

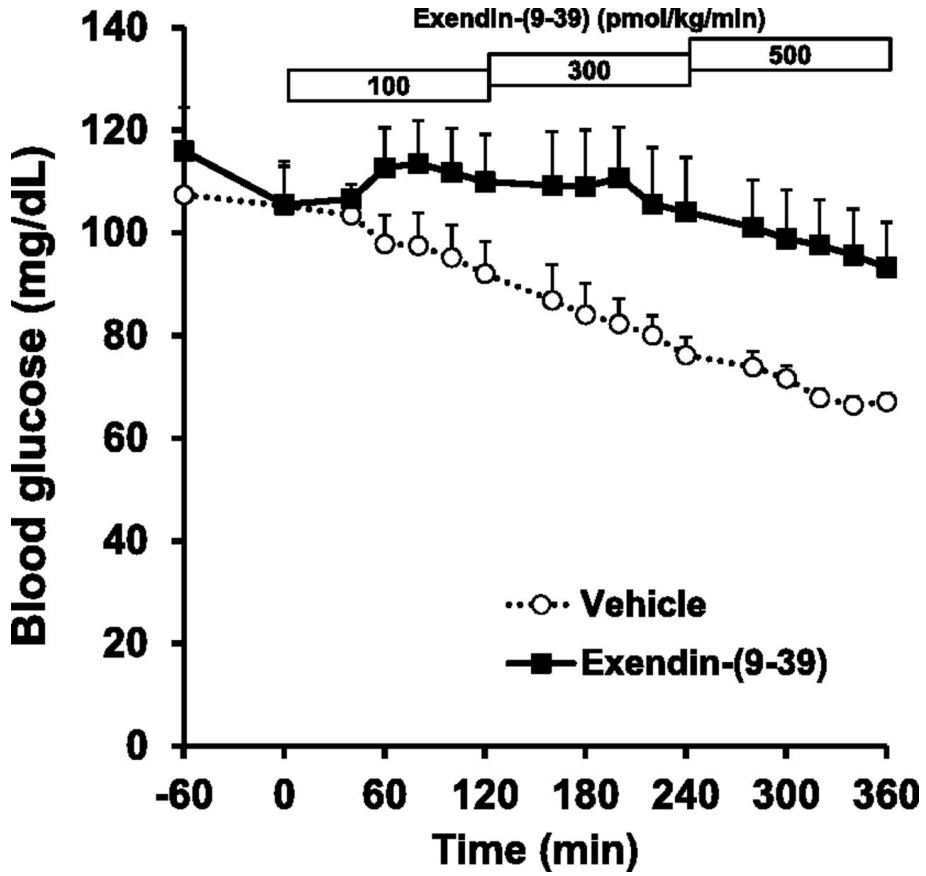

Brain
Neuroprotection
Appetite
Heart
Cardioprotection
Cardiac function
Intestine
Stomach
GLP-1
Gastric emptying
Liver
Glucose production
Pancreas
Insulin sensitivity
Insulin secretion
Glucagon secretion
Insulin biosynthesis
β-cell proliferation
β-cell apoptosis
Adipose tissue
Muscle
Glucose uptake and storage

Exendin (9-39)

- Specific GLP-1 receptor antagonist
- Normalizes fasting hypoglycemia in SUR-1(-/-) mice by reducing insulin secretion
- Randomized, open-label, crossover study: 9 K(ATP)HI patients received either exendin-(9-39) or vehicle on two different days; **mean nadir blood glucose and glucose AUC were significantly increased by exendin-(9-39)**
- Exendin-(9-39) significantly inhibited amino acid-stimulated insulin secretion in pancreatic islets from neonates with K(ATP)HI

Diabetes. 2012 Oct;61(10):2585-91. Epub 2012 Aug 1. GLP-1 receptor antagonist exendin-(9-39) elevates fasting blood glucose levels in congenital hyperinsulinism owing to inactivating mutations in the ATP-sensitive K+ channel. Calabria AC1, Li C, Gallagher PR, Stanley CA, De León DD

Mean fasting blood glucose ± SEM during vehicle and exendin-(9-39)



Diabetes. 2012 Oct;61(10):2585-91. Epub 2012 Aug 1. GLP-1 receptor antagonist exendin-(9-39) elevates fasting blood glucose levels in congenital hyperinsulinism owing to inactivating mutations in the ATP-sensitive K+ channel. Calabria AC1, Li C, Gallagher PR, Stanley CA, De León DD.

Pasireotide

- Newer somatostatin analogue – more specific binding to **SSTR5**
- Inhibition of **insulin secretion: SSTR2 and SSTR5**
- Inhibition of **glucagon secretion: SSTR2**
- Octreotide inhibits both insulin and glucagon secretion but Pasireotide suppresses predominantly only insulin
- Used in adults for Cushing's disease and PPHH – not currently used in children for any medical indication
- Small pilot study to assess the effect of s/c Pasireotide on preventing hypoglycemia due to hyperinsulinism was proposed in >18 years (?study withdrawn…as per Clinical Trials website)

CRN02481 (Crinetics Pharmaceuticals)

- New class of **oral selective nonpeptide somatostatin [SST5] agonist**
- Inhibits insulin secretion while avoiding glucagon suppression
- In rats treated with CRN02481 - blood glucose normalised and at higher doses, hyperglycaemia was noted
- Optimizing the good manufacturing process [GMP], synthesis and performing good laboratory practice [GLP]
- Planned for initiating **Phase 1** human proof-of-concept clinical trial that evaluates inhibition of insulin secretion and its effects on blood glucose in **2019**

RZ358 (Rezolute)

- **Intravenous human monoclonal antibody** - counteracts the effects of hyperinsulinemia via allosteric modulation of INSR
- Reverses hypoglycemia in hyperinsulinemic mice and rats
- Increases PP glucose and induces insulin resistance in adults
- Single dose **IV XOMA 358** in CHI patients >12 years – increased fasting and postprandial glucose [hypo reduced by nearly 50%]
- Demonstrated proof-of-concept and safety in Phase 2a studies
- **RZ358** has received designated orphan status in the US & EU
- Rezolute plans to advance clinical development

Novel Soluble Glucagon(s)

- Glucagon - useful in acute phase to stablise blood glucose (IV/SC/IM) but not stable in aqueous solutions
- Available as lyophilized powder - once reconstituted - begins to degrade and fibrillate rapidly
- Unstable and unsuitable for use long term use in pumps

<u>Newer Soluble Glucagon Preparations</u>

- **Dasiglucagon (Zealand pharma)**
- **CSI-Glucagon™ (Xeris Pharma)**
- **AmideBio**

Dasiglucagon (Zealand pharma)

- Glucagon analog with improved solubility and stability
- Single dose: Phase 2 – in T1DM with hypo - achieved glucose increases of >20 mg/dL within a median time of 9-10 mins – safe and tolerated – Phase 3 underway
- Mutli-dose: Phase 2a studies – in **dual-hormone artificial pancreas system in T1DM** (with Beta Bionics) – effective, safe and well tolerated; Phase 2b (longer duration) planned
- Received a positive opinion on orphan medicinal product application in US and EU

CSI-Glucagon™ [Xeris Pharma]

- Stable Non-Aqueous Glucagon for Severe Hypoglycemia
- Effective and safe in adults with experimental hypoglycemia
- Phase 3 studies to be undertaken for developing the ready-to-use glucagon auto-injector for hypoglycemia
- **S/c infusion using Omnipod pump** for 48hrs – recruiting for Phase 2 (proof of concept) multi-center, randomized, placebo-controlled, double-blind trial - to assess the efficacy in children < 1 year of age with CHI
- Expected completion Jan 2019

Conclusions

- **Diazoxide** – first line of therapy

Diazoxide unresponsive: rapid genetic testing

- **Focal** – DOPA PET CT, Surgery
- **Diffuse** – medical (octreotide, novel therapies) or surgery

- ***Newer/Futuristic medical options…***

Thank You

Alder Hey Children's Hospital, Liverpool, UK